UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/216,506	03/22/94	SCHLEGEL	C 010091001

EXAMINER
CAPUTA, A

ART UNIT	PAPER NUMBER
1813	18

18N1/0908

ROBIN L. TESKIN
BURNS, DOANE, SWECKER & MATHIS
P.O. BOX 1404
ALEXANDRIA, VA 22313-1404

DATE MAILED: 09/08/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6/3, 6/6, 6/13/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892. 2pgs
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 1pg - Paper No. 14
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-26, 41-49 are pending in the application.
   Of the above, claims 4-9, 41-45, 48, and 49 are withdrawn from consideration.
2. ☒ Claims 27-40 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 10-26, 47, and 46 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. Applicants' amendment and declarations were received and been have entered. Claims 27-40 have been canceled. Claims 1-26, and 41-49 are pending.

Election/Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I Claims 1-3, 10-26, 46, and 47, are drawn to a recombinantly produced L1 protein, vaccine comprising said protein, method of using the vaccine, classified in Class 424, subclass 89.

Group II Claims 4-9, 41-45, drawn to vector comprising the DNA encoding the L1 protein, host, and method of making the protein using the DNA, classified in Class 435, subclass 69.3.

The inventions are distinct, each from the other because of the following reasons:

3. Inventions I and II are related as a product made and process of making. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the product of Invention I can be made by Merrifield chemical synthesis. Inventions I drawn to polypeptide and Invention II drawn nucleic acid are distinct since they are products with different structure and biological properties. The polypeptides are made of amino acids whereas the claimed DNA acid are made of nucleotides. Methods known in the art used to make the polypeptide require different reagents and parameters from the

methods of making DNA encoding the protein and the method of making the polypeptide does not require the DNA.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Donna M. Meuth on July 22, 1994 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-3, 10-26, 46, and 47. Affirmation of this election must be made by applicant in responding to this Office action. Claims 4-9, 41-45, 48, and 49 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Information Disclosure Statement

7. References cited in the specification have not been considered unless otherwise made record in the case. See 37 CFR 1.97-1.99 and M.P.E.P. 609.

Specification

8. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed (L1).

Claim Rejections - 35 USC § 112/2nd paragraph

9. The prior rejection of claims 1-26 and 41-49 under 35 U.S.C. § 112, second paragraph (see Paper No. 10, page 12) is withdrawn in view of applicants' amendment.

10. Claims 1-3, 10-26, 46, and 47 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is vague and indefinite since it is unclear if applicant intends to claim a recombinant produced fragment (i.e a portion of the L1 protein and/or a recombinantly produced L1 protein-See claim 1), particularly in view that dependent claims 2, 3, 10, 11, and 46, and 47 are claiming a protein and not a fragment. Further claim 1 is rejected since there is lack of antecedent basis for said protein.

b. Claims 1-3, 10-26, 46, and 47 are rejected for using the term capable. It is not clear if the capability to reproduce the antigenicity is a limitation to the claimed invention.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

12. Claims 1-3, 10-12, and 15-18 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to a non-statutory subject matter.

The claimed L1 protein produced recombinantly or the vaccine comprising said protein have the same characteristics and utility as protein found naturally and therefore does not constitute as patentable subject matter. In the absence of the hand of man, naturally occurring proteins are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Mere purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck Co. v. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintegrating Co., 90 US 566 (1974); American Fruit Growers v Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. v. Kalo Innoculant Co. 33 US 127 (1948). Filing of evidence of a new utility imparted by the increased purity of the claimed invention and amendment to the claims to recite the essential purity of the claimed proteins is suggested to obviate this rejection. For example, "A purified ...protein...". The recitation of the term "recombinant" to the claim fails to impart an character to the protein which one of skill in the art could recognize and find protection from infringing the instant claims based thereupon" The law is well settled that while a product by process claim is limited and defined by the process of determination of patentability is based on the product itself. In re Brown 459 F. 2d 531, 535, 173 USPQ 685, 688 (CCPA 1972), as cited in In re Thorpe, 77 F. 2d 695, 227 USPQ 964 (CAFC, 1985).

13. Claims 15-26 are rejected under 35 U.S.C. § 101 because the claimed invention as disclosed lacks patentable utility.

The specification provides insufficient evidence that recombinantly expressed produced L1 protein or antigenic fragment thereof of HPV can prevent papillomavirus (PV) infection in humans.

The claimed invention is drawn to a L1 protein of HPV for the prevention of papillomavirus infection in humans. Evidence provided is directed to the use of sera from various hosts (i.e. human, rabbit, etc.) in the ability to control the cyst induced by BPV-1, bovine papillomavirus type 1 virus (see Tables 1, 11). Human sera which reacts with conformational and linear epitopes of BPV-1 did not result in the reduction of cyst (see specification, page 28). It would appear that the animal model using BPV-1 provides insufficient guidance if conformational epitopes of a recombinant L1 protein of HPV are protective in humans. Further, it would not have been expected that the ability L1 of BPV to protect from infection of BPV can be used to predict the outcome of L1 of HPV to protect HPV infection since from the prior art at the time of the invention (see Jarrett et al. Vet. Record 126:473-475 May 1990) one type of BPV does not protect another type of BPV.

Case law has been established that a patent may not be granted on a composition unless a utility is shown other than for experimental purposes only. The burden is on the applicant to demonstrate that the claimed products posses the claimed biological activity. See Brenner v Manson 383 U.S. 519, 148 USPQ 689 (1966). Further it is well established that a patent may not be granted on a chemical compound unless the data is such as to convince one of ordinary skill in the art that the proposed utility is sufficiently established. See In re Ironis, 340 F. 2d 924, 144 USPQ 351 (CCPA 1965); Ex parte Kreplka 231 USPQ 746 (PTO Bd. Pat. Appls & Interf. 1986); Ex parte Chwang, 231 USPQ 751 (PTO Bd. Pat. Appls & Interf. 1986).

The declarations under 37 C.F.R. § 1.132 filed by Drs. Schlegel, Cossman, Pearson are insufficient to overcome the rejection of claims 15-26 under U.S.C. § 101 rejection and 35 U.S.C. § 112, first paragraph (a).

Schlegel (see item 4), Pearson (see items 5, 6, 8-10), Cossman (see items 5, 6, 8-10) state the *in vitro* assays are used to establish the *in vivo* efficacy of putative papillomavirus immunogens or immunizing compositions. Further Schlegel states the HPV L1 proteins are useful as a vaccine since there is extensive similarity between HPV and COPV, and COPV L1 protects beagles from dogs (see item 4-5 and Experiments 1 and 2). Pearson and Cossman provides statements to support evidence of using the L1 of COPV as evidence for the predicting the outcome of using the HPV in humans (see item 11).

With respect to using *in vitro* assays it is the Examiner's position that the *in vitro* assays are not sufficient to predict the outcome using the HPV L1 in humans. The statements presented by applicants are only conclusionary with no data to support said statements. Further, since on the record (see Grant Application by R. Schlegel, page 29) and in the art at the time of the invention (see Jarrett) it is taught that there are no tissue culture to grow HPV, the protection of papillomavirus is type specific (see Jarrett), and there are no animals into which HPV can be introduced (see page 29 of the Grant Application of R. Schlegel) it would not be expected that an *in vitro* assays using BPV as described in the specification, or as stated in the declarations is sufficient to determine the use of HPV L1 protein as a vaccine. With respect to using the COPV virus as a means to predict the outcome of using the HPV L1 as a vaccine. It is the Examiner's position that applicant statements are only conclusionary with no evidence that the COPV is useful to predict the outcome of using the L1 of HPV as a vaccine in humans.

Applicants have not provided sufficient evidence that the L1 of HPV and COPV are similar. There is no evidence that the protective epitopes of the L1 are shared between the COPV and HPV. Additionally, the art at the time of the invention teach not all types of papillomavirus which infect a homologous host appear to be similar. Jarrett et al. teach one type of BPV does not protect a second BPV in cattle. Further Kremsdorf et al. teach several HPVs' which are not similar to other HPV's. Accordingly, since the various types of papillomaviruses which infect a homologous host appear not to be similar it is unclear how a PV of one host can predict the outcome of a PV in a second host. Furthermore, the declaration are not persuasive since there is no evidence that the protective epitopes of the L1 are shared between the COPV and HPV.

Evidence that the L1 protein of the HPV-1 is reactive with monoclonal antibodies which recognize conformational epitopes is not evidence that L1 of HPV-1 is protective. The specification provides no evidence that the epitopes which are protective are conformational epitopes, and secondly it is not clear that with active immunization the protective epitopes are maintained to elicit a protective immune response. Finally it is not clear that the antibody response to protective epitopes is high enough to provide protection in vivo.

Claim Rejections - 35 USC § 112/1st paragraph

14. The prior rejection of claims 1-3, 10-26, 46, and 47 under 35 U.S.C. § 112, first paragraph (e-See Paper No. 7, page 8) is withdrawn in view of applicants' amendment.

15. The prior rejection of claims 1-3, 10-26, 46, and 47 under 35 U.S.C. § 112, first paragraph (b) is withdrawn in view of further consideration by the Examiner.

16. The prior rejection of Claims 1-26 and 41-49 under 35 U.S.C. § 112, first paragraph (see Paper No. 9, page 13) and prior objection to the amendment received 6/10/93 (see Paper No. 8) under 35 U.S.C. § 132 is withdrawn in view of applicants' amendment.

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. The prior rejection of claims 1-3, 10-26, 46, and 47 under 35 U.S.C. § 112, first paragraph (a) and (c) is maintained.

a. The specification is not enabled for the use of the claimed invention because the utility of the invention has not been proven for the same reasons outlined in the rejection under 35 U.S.C. § 101.

c. Applicants have argued given the information in this application one could identify those portions capable of binding to conformation specific epitopes.

Applicants arguments are not persuasive. The specification provides insufficient guidance as to which fragments of the claimed L1 capsid are useful for the protection of PV and are capable of reproducing the antigenicity of the L1 expressed on the intact virus. It would be expected that portions of the protein which are hydrophobic would be poorly immunogenic and not useful for the detection and/or protection of PV. Further prior art at the time of the invention predicts with no certainty which portions are antigenic. Stern teaches of the problems of predicting antigenic sites on proteins. Stern teaches that one

problem of predicting antigenic sites is whether all antigenic sites on the protein in question have been found (see page 166, Column 2 and 3) and that the sequence alone is not necessarily a determinant of immunogenicity (see page 167). Berzofsky teaches that although intrinsic factors (i.e. hydrophilicity and mobility) may determine the repertoire of potential antigenic sites, only a subset of these sites will elicit antibodies (see page 937, Column 1 and 2). Additionally there are positions in the sequence critical to the protein's structure/function relationship, e.g. such as various positions or regions directly involved with binding. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., Science, Vol 247, pp 1306-1310, especially p. 1306, column 2, paragraph 2 and Kumar et al., PNAS 87: 1337-1341, 1990). Because not all portions can be predicted it would require undue experimentation to determine which fragments of the L1 protein as broadly claimed are useful.

19. The prior rejection of claims 1, 10, 12-14, 18-21, and 25 under 35 U.S.C. § 102(b) as being anticipated by Danos et al is withdrawn upon further consideration by the Examiner.

20. The prior rejection of claims 1-26 and 41-49 under 35 U.S.C. § 103 as being unpatentable over Christensen et al., Pilacinski et al., Sambrook et al. and Danos et al. is withdrawn upon further consideration by the Examiner.

New Grounds of Rejection

21. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and use the claimed invention, i.e. failing to provide an enabling disclosure.

f. The specification provides insufficient guidance for using a L1 as broadly claimed. Since the specification provides insufficient guidance to the DNA sequence of the L1 protein of the PV's as broadly claimed, the homologous region(s) of the L1 which are useful for cloning the L1 of other PV's, and not all PV are homologous (see Kremsdorf et al.) it would appear that it would be an undue burden to clone the L1 of the PVs' as broadly claimed. For support of the Examiner's position applicants are directed to *Fliers v. Sugano,* 25 USPQ 2d 1601 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., and Genetics Institute., Inc.,* 18 USPQ 2d 1016 (Fed. Cir. 1991). Further since not all PV's share homology and it known that the protection of papillomavirus is type specific (see Jarrett et al.) it is unpredictable as to whether the L1 protein of the PV's as broadly claimed are useful as a vaccine.

g. The specification provides evidence of expressing the L1 in cos cells. The specification further states the use of baculovirus. However, the specification provides insufficient guidance to a protein produced recombinantly as broadly claimed which has properties of the antigenicity of the L1 of the intact virion and useful as a vaccine. As stated on the record (see declarations of Pearson [item 13; pages 6 and 7] and Cossman [item 13; pages 6 and 7] there is a high level of unpredictability associated with expressing viral proteins in a native conformational correct form. Accordingly given the statements from the declaration it appears that it is unpredictable as to whether expressing the L1 recombinantly as broadly claimed (i.e baculovirus or other eucaryotic systems) would express the protein in the native correct form and be sufficiently immunogenic to confer immunity.

22. Claims 1-3, 10-26, 46, and 47 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

23. Claims 1-3, 10-26, 46, and 47 are rejected under 35 U.S.C. § 103 as being unpatentable over Pilacinski et al., and further in view of Sambrook et al., Danos et al., Schwarz et al., Cole et al.(1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (US Patent No. 4,551,270)

Pilacinski et al. teach fused proteins of L1 and L2 BPV-1 cloned and expressed in E. coli. Pilacinski et al. teach although the antisera generated against the fusion proteins react specifically with BPV-1 to be useful as a vaccine the proteins must elicit an immunological immune response that prevents infection (see page 359, lines 1-5). Pilancski et al. teaches that one indication is the ability of the of the antisera to neutralize the virus *In vitro*. Pilacinski et al. teach that "the L1 encoded epitope produces a stronger and more consistent response" (see page 359, Column 1, last two lines) and "The evidence for neutralizing epitopes ... within L2 is considerably weaker than for L1 (see page 359, Column 2, paragraph 3). Pilacinski et al. further teach (see page 359, Column 2 and page 360, Column 1) a majority of the BPV-1 specific antigenic sites were not presented to the immune system in animals and this could be due to non-natural conformation of the BPV portion. Pilacinski et al. teach (see page 360, last paragraph) beta-gal fusion proteins often are insoluble forming aggregates. Pilacinski et al. does not teach of expressing the L1 protein using mammalian cells to provide a L1 protein which is protective.

Sambrook et al. teaches (see page 16.3) that one problem of expressing proteins in bacteria are that they are folded

incorrectly and consequently exhibit low specific activities. Sambrook et al. teach a solution is the expression of proteins in mammalian cells such as SV40 and baculoviruses. Sambrook et al. teach of several plasmid SV vectors that can be used to express the protein of interest in cos cells. It would have been obvious to one of ordinary skill in the art at the time of the invention to express the L1 protein using the method described by Sambrook et al. since it would have been expected that with the use of baculoviruses and SV40 plasmid vectors known in the art at the time of the invention would fold correctly.

Pilancski et al. does not teach of using the L1 of other PV's as a vaccine.

Danos et al. teach the DNA sequence encoding the L1 of HPV1a. Schwarz et al. teach the DNA sequence encoding the L1 of HPV6b. Cole et al. (1986) teach the DNA sequence encoding the L1 of HPV33. Seedorf et al. teach the DNA sequence encoding the L1 of HPV16. Cole et al. (1986), Schwarz et al. further teach the strong identity (i.e. homology) of the DNA encoding the L1 of the various PV's. Baker et al. teach of the DNA sequences of the L1 of various papillomaviruses and the that DNA sequences of various papillomaviruses are available (see whole document especially page 321, Figure 17. Baker et al. teaches of using methods known in the art to determine the ORF's of particular protein including L1. Baker et al. teaches the L1 are the most highly conserved of the papillomavirus proteins (see page 379, first paragraph). Cole et al. (1987) teaches of the DNA sequence of the L1 of HPV 18 and homology of the L1 of the various PV's

It would have been obvious to one of ordinary skill in the art that the recombinant L1 of other PV's from the DNA encoding the L1 of the respective PV's as taught by Danos et al., Schwarz et al., Cole et al. (1986 or 1987), Seddorf et al., Baker et al., and other selected types of PV's known in the art would protect

against the respective PV since Pilancksi et al. teach using a vaccine composition comprising L1 from the papillomavirus BPV and Cole et al. (1986 and 1987), Baker and Schwarz et al. teach of homology of the L1 within the various papillomaviruses. Further it would have been further obvious to one of ordinary skill in the art to include a vaccine composition which contain the L1 of several types of PV since one would have been motivated to provide protection against several types of PV described in the art.

Danos et al. (US Patent No. 4,551,270) teach (see Column 6) L1 peptides coupled to a carrier such as serum albumins preferably animal when it relates to vaccines intended for veterinary use. It would have been obvious to couple L1 with serum albumins as described by Danos et al. (US Patent No. 4,551,270) such as bovine serum albumin, a serum albumin well known in the art to enhance immunogenicity of the L1.

Applicants' argued and now present in declaration form (see Pearson and Cosmann-items 13 and 14) that it would not expected that the L1 would be folded correctly when expressed in mammalian cells and substantially reproduce the antigenicity of the intact PV virion. This is not persuasive in view that Sambrook et al. teach (see page 16.3) that one solution of expressing proteins in bacteria which are folded incorrectly and consequently exhibit low specific activities, is the expression of proteins in mammalian cells such as SV40 and baculoviruses.

Applicants' argued and now present in declaration form (see Pearson and Cosmann-items 13 and 14) that the L2 protein might have been necessary for the antigenicity of L1 and the applicant's invention is the first to provide evidence that L1 by itself may provide protection. This is not persuasive in view that claimed subject matter is drawn to a recombinant L1 protein

which is capable of substantially reproducing the antigenicity of the intact virions, the recombinant L1 protein as claimed encompasses a fusion protein of L1 and L2, the vaccine claims do not exclude the L2, and of the teachings of Danos and/or Pilacinski et al. Further Danos discloses that peptides of L1 are protective and Pilacinski et al. teaches that proteins useful as a vaccine must elicit an immune response, such as L1 which produces a stronger and more consistent response than L2 (see page 359, Column 1, last paragraph).

24. Claims 1-3, 10-12, 15, 18, 46, and 47 are rejected under 35 U.S.C. § 103 as being unpatentable over Zhou et al (J. Virology 185: 251-257 November, 1991).

Zhou et al (J. Virology 185: 251-257 1991) teach a recombinant HPV 16 L1 protein expressed recombinantly by vaccinia. Zhou et al. teach the vaccinia comprising the L1 protein produced virus-like particles. Zhou et al. teach said particles possessed a similar appearance to that of the papillomavirus. Zhou et al. does not characterize the papillomavirus as reproducing the antigenicity of the L1 protein expressed of the intact virus. However, it is reasonable for one of ordinary skill in the art to expect that the recombinant L1 protein as claimed it is able to reproduce the antigenicity of the L1 protein of the intact virion since the Zhou et al. teach that the vaccinia comprising the L1 protein is able to form virus like particles with a similar appearance to that of papillomavirus.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not

possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Further, although the reference appears to disclose the same product claimed by applicants, the reference does not disclose the products produced by the claimed process (i.e. recombinantly expressed in baculovirus and cos cells). However, the production of a product by a particular process does not impart novelty or unobviousness to a product when the product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner.

See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

Therefore even if a particular process used to prepare a product unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art.

See In re King, 107 F. 2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F. 2d 599, 601, 38 USPQ 143-45 (CCPA 1938); In re Bergy, 563 F. 2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) vacated 438 US 902 (1978); and United States v. Ciba-Geigy Corp, 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

Since Zhou et al. directly suggests using the HPV-like particles comprising the L1 of HPV-16 as a vaccine (see abstract) it would have been obvious to one of ordinary skill in the art to use said composition as a vaccine.

25. Claims 1-3, 10, 11, 46, and 47 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35

U.S.C. § 103 as obvious over Zhou et al. (J. Gen. Virology 71: 2185-2190, 1990).

Zhou et al. teach a L1 protein of HPV-16 expressed in recombinant vaccinia in human infected cells. Zhou et al. does not characterize the L1 protein as having the same antigenicity of the L1 of the intact virion. However, since both the broadly claimed L1 protein and L1 taught in the prior art are produced recombinantly and produced in a mammalian host cell it is reasonable to conclude that the L1 as taught in the prior art is the same or an obvious or analogous variant of the L1 as claimed.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Further, although the reference appears to disclose the same product claimed by applicants, the reference does not disclose the products produced by the claimed process (i.e. recombinantly expressed in baculovirus and cos cells). However, the production of a product by a particular process does not impart novelty or unobviousness to a product when the product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner.

See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

Therefore even if a particular process used to prepare a product unobvious over the prior art, the product per se, even

when limited to the particular process, is unpatentable over the same product taught by the prior art.

See In re King, 107 F. 2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F. 2d 599, 601, 38 USPQ 143-45 (CCPA 1938); In re Bergy, 563 F. 2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) vacated 438 US 902 (1978); and United States v. Ciba-Geigy Corp, 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

26. Claims 1-3, 12, 19, 46, and 47 are rejected under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Lin et al. (Virology 187(2): 612-619, April 1992).

Lin et al. teach a L1 protein of a cottontail rabbit papillomavirus expressed in recombinant vaccinia transfected BHK cells (see page 613; column 2). Lin et al. teaches of vaccinating NZW rabbits intradermally with 1 X 10^6 PFU of the recombinant L1 vaccinia virus at multiple sites. Lin et al. discloses of boosting 1 month later with the same dose (see page 614; column 1). Lin et al. disclose that said composition is protective in rabbits (see pages 165 and 616). Lin et al. does not characterize the L1 protein as having the same antigenicity of the L1 of the intact virion. However, since both the broadly claimed L1 protein and L1 taught in the prior art are produced recombinantly and produced in a mammalian host cell and both are protective it is reasonable to conclude that the L1 as taught in the prior art is the same or an obvious or analogous variant of the L1 as broadly claimed.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not

possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Further, although the reference appears to disclose the same product claimed by applicants, the reference does not disclose the products produced by the claimed process (i.e. recombinantly expressed in baculovirus and cos cells). However, the production of a product by a particular process does not impart novelty or unobviousness to a product when the product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner.

See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

Therefore even if a particular process used to prepare a product unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art.

See In re King, 107 F. 2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F. 2d 599, 601, 38 USPQ 143-45 (CCPA 1938); In re Bergy, 563 F. 2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) vacated 438 US 902 (1978); and United States v. Ciba-Geigy Corp, 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

27. Claim 13, 14, 16, 17, 19-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Zhou et al. (J. Virology 185: 251-257 1991) as applied to claims 1-3, 10-12, 15, 18, 46, and 47 above, and further in view of Danos et al., Schwarz et al., Cole et al.(1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (US Patent No. 4,551,270).

28. Claim 13-18, 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Lin et al. (Virology 187(2): 612-619, April 1992) as applied to claims 1-3, 12, 19, 46, and 47 above, and further in view of Danos et al., Schwarz et al., Cole et al.(1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (US Patent No. 4,551,270).
29. Claim 12-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Zhou et al. (J. Gen. Virology 71: 2185-2190, 1990) as applied to claims 1-3, 10, 11, 46, and 47 above, and further in view of Danos et al., Schwarz et al., Cole et al.(1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (US Patent No. 4,551,270).

Zhou et al. ('90 or '91) nor Lin et al. not teach of using the L1 of other PV's as a vaccine, nor using as a carrier BSA or KLH.

Danos et al. teach the DNA sequence encoding the L1 of HPV1a. Schwarz et al. teach the DNA sequence encoding the L1 of HPV6b. Cole et al. (1986) teach the DNA sequence encoding the L1 of HPV33. Seedorf et al. teach the DNA sequence encoding the L1 of HPV16. Cole et al. (1986), Schwarz et al. further teach the strong identity (i.e. homology) of the DNA encoding the L1 of the various PV's. Baker et al. teach of the DNA sequences of the L1 of various papillomaviruses and the that DNA sequences of various papillomaviruses are available (see whole document especially page 321, Figure 17. Baker et al. teaches of using methods known in the art to determine the ORF's of particular protein including L1. Baker et al. teaches the L1 are the most highly conserved of the papillomavirus proteins (see page 379, first paragraph). Cole et al. (1987) teaches of the DNA sequence of the L1 of HPV 18 and homology of the L1 of the various PV's

It would have been obvious to one of ordinary skill in the art that the recombinant L1 of other PV's from the DNA encoding

the L1 of the respective PV's as taught by Danos et al., Schwarz et al., Cole et al. (1986 or 1987), Seddorf et al., Baker et al., and other selected types of PV's known in the art would protect against the respective PV since Zhou (90 or 91) or Lin et al. teach using a vaccine composition comprising L1 from a particular papillomavirus and Cole et al. (1986 and 1987), Baker and Schwarz et al. teach of homology of the L1 within the various papillomaviruses. Further it would have been further obvious to one of ordinary skill in the art to include a vaccine composition which contain the L1 of several types of PV since one would have been motivated to provide protection against several types of PV described in the art.

Danos et al. (US Patent No. 4,551,270) teach (see Column 6) L1 peptides coupled to a carrier such as serum albumins preferably animal when it relates to vaccines intended for veterinary use. It would have been obvious to couple L1 with serum albumins as described by Danos et al. (US Patent No. 4,551,270) such as bovine serum albumin, a serum albumin well known in the art to enhance immunogenicity of the L1.

Thus the claimed invention as a whole is clearly prima facie obvious, in the absence of evidence to the contrary.

30. The use of the trademarks such as Tween 20 (see page 44), Immunolon II (see page 44), Dynatech (see page 44) , Express ^{35}S Protein labelling Mix (see page 46), Elvanol (see page 47), Olympus (see page 47) has been noted in this application. These and other trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

31. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ghim et al. (Virology 190: 548-552 September 1992) teach (see abstract) of polyclonal and monoclonal antibodies which react specifically with conformational epitopes of the HPV-1 L1 protein. Ghim et al. teach the screening of capsid protein of PV for reactivity with conformation dependent antibodies represents a method to ensure that such proteins will be suitable for vaccine development or detection of human PV infections.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Anthony C. Caputa, whose telephone number is (703)-308-3995. The examiner can be reached on Monday-Thursday from 8:30 AM-6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Ms. Christine Nucker, can be reached on (703)-308-4028

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703)-308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4227.

Anthony C. Caputa, Ph.D.
August 17, 1994

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180